UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Offic
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/205,096	12/03/98	DRACHMAN	D 01107.77737

BANNER & WITCOFF
1001 G STREET N W ELEVENTH FLOOR
WASHINGTON DC 20001-4597

HM22/0713

EXAMINER	
SORBELLO,E	
ART UNIT	PAPER NUMBER
1633	15

DATE MAILED: 07/13/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

PTO-90C (Rev.11/00)

1- File Copy

Office Action Summary	Application No.	Applicant(s)	
	09/205,096	DRACHMAN, DANIEL B.	
	Examiner	Art Unit	
	Eleanor Sorbello	1633	

-- The MAILING DATE of this communication appears on the cover she t with th correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 April 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41-67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

R sponse t amendment

1. Applicant's (1) amendment and Request for reconsideration and (2) Declaration, in response to the official Office Action mailed December 6, 2000 as Paper No. 13, has been received and filed on April 26, 2001 as Paper No. 14. Claims 41-67 are pending. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's argument.

2. Applicant's arguments are addressed below on a per section basis. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

3. Claims 41-67 stand rejected under 35 USC § 112, first paragraph for reasons of record. Applicant's arguments have been fully considered but they are not persuasive.

Applicants argue (on page 2 of Response dated 4/26/01) that an *ex vivo* strategy of gene transfer is not unpredictable and that the considerations regarding the state of the art of *ex vivo* therapy does not apply to the specific facts of the instant invention. They also argue that *ex vivo* clinical trials have demonstrated the presence of treatment for specific periods of time. The results of the ex vivo experiments quoted by applicants in Crystal's reference (see Response page 3, paragraph 3) in which applicants quote that the gene expression is observed for extended periods of time. However, the instant

invention is directed to the ablation of T cells specific for auto antigens, and is therefore non-analogous to the examples cited by applicants. Examiner contends that the prior art on *ex vivo* therapy referred to by applicants is directed to gene supplementation. The instant application is drawn to immunotherapy wherein T cells specific for antigens developed by a patient against its own antigens are ablated when APC cells transfected with FasL and FADD according to instant invention are subsequently administered to the patient.

Applicants argue that examiners contention that *in vivo* gene transfer for targeting specific cells is of no relevance in the current invention, because they have exemplified this in cell culture, implying that the ex vivo strategy of introducing a nucleic acid into a cell is conducted *in vitro* and therefore enabled. However, examiner maintains that the APC cells transfected with a nucleic acid are eventually introduced into a patient and therefore, subjected to an environment in the patient which is entirely different to that in cell culture. Therefore, even though some *ex vivo* experiments are in clinical trials, *ex vivo* gene therapy is not enabled across the board. Crystal et al. discuss the obstacles to successful human gene transfer (See page 409, col. 1) and the inconsistent results observed in ex vivo clinical trials. For instance Crystal described two children afflicted with ADA and receiving autologous T cells which were modified ex vivo with normal ADAcDNA. The normal ADA+ cells varyied between 0.1-60%. Additionally, even though successful transfer of the ADA gene to the epithelium is observed successful expression is only observed in 5% of the cells.

Applicants argue that the use of prophetic language is permissible, and that this does not establish or confirm a lack of enablement. (See page 4 of Response dated 4/26/01). However, examiner contends that prophetic language is permissible in those applications where unpredictability is not a factor to consider. Applicants state that they have exemplified that expression of the gene takes place *in vitro* cell culture, and there is no reason to believe that it would not take place *in vivo*. However, as discussed above, a APC or any cell that reacts in a specific manner in a cell culture environment may not react in a similar manner when placed in a patient's body. In view of the breadth of the claims directed to a method for ablating auto-antigen specific T cells in a patient with an auto-immune disorder, it is not clear that the APC cells removed from the patient and transfected with a polynucleotide encoding at least a portion of AchR and FasL and FADD will simulate that which occurs in a lymphoma cell line transfected ex vivo. Additionally, it is not clear that the APCs transfected with AchR, will inactivate the AchR specific T cells rather than stimulate them. Also, how is one to know how much is to be administered taking into consideration that the patient has an auto immune disorder and already has activated T cells. The specification does not teach one where and how to obtain the DNA encoding auto antigens and if the AchR will simulate auto antigens in any patient afflicted with any auto immune disorder. The other factors that will play a part in the *in vivo* method of ablating T cells that do not have guidance in the specification are: how one is to obtain enough APCs from the patient and what is the generic "product" claimed in the instant invention which is detrimental to the activated T cells. Therefore in view of the unpredictability in administering a nucleic acid to a cell ex

vivo and subsequently administering the transfected cells to a patient as evidenced by the state of the art, the breadth of the claims and lack of guidance in the specification, one of skill in the art will not expect the results obtained from *in vitro* cell culture to be suggestive of *ex vivo* experimentation.

Applicants also argue that they do not have to reduce to practice each and every viral vector. Applicants teach that VVV and plasmids transfect into APCs effectively and which induce a high level of expression of an antigen FasL and truncated FADD, which is sufficient to enable complete targeting and killing of T cells in cell culture. Applicant states that there is no reason to doubt that applicants are enabled for the ability to use viral vectors such as VVV for *in vitro* transfection, into APC (See page 5, ¶ 3, of Response).

The declaration under 37 CFR 1.132 filed April 26, 2001 is insufficient to overcome the rejection of claims 41-67 based upon treatment of patients with an autoimmune disease as set forth in the last Office action and discussed herein. Examiner agrees that applicants have demonstrated via the declaration that VVV comprising the following genetic elements, (1) AchR (AA 1-210), (2) FasL and (3) truncated FADD, transfected into APCs effectively and which induced a high level of expression of an antigen FasL and truncated FADD, which was sufficient to enable complete targeting and killing of T cells in cell culture. However, the claims are directed to treatment of patients and as stated above, applicants are not enabled for *in vivo* applications of the above, due to the following: The claims are directed to treatment of a patient with an autoimmune disorder. Therefore, the introduction of a viral vector,

unless completely gutted, will respond by eliciting an immune response opposing and contrary to the intent of the instant application. The field of gene therapy via administration of viral vectors is unpredictable and the choice of viral vectors depend on the specific treatment. Therefore, in view of the breadth of the claims directed to any viral vector, and unpredictability as suggested by the state of the art, it is not clear that applicants are enabled for that which is claimed. Additionally, some claims do not recite the requirement of FADD for protection of introduced cells against destruction. It is not clear how these transfected cells comprising FasL will behave in a patient with an autoimmune disorder. Applicants did not teach when and how to administer APCs transfected with (1) AchR (AA 1-210), (2) FasL and (3) truncated FADD, to a patient with an auto-immune disease. Additionally, it is not clear that this one example wherein the epitopes of an α-subunit of a torpedo acetyl choline receptor are used *in vitro* experiments represent all autoantigens of patients with autoimmune disorders. Also, the one example (FasL) used in the *in vitro* experiments as a product that is detrimental to activated T cells representative of all products detrimental to activated T cells as claimed? Therefore the one example used in these experiments are not commensurate in scope to all autoantigens and all products detrimental to activated T cells as broadly claimed. Therefore, in view of the unpredictability, state of the art and breadth of the claims applicants are not enabled for ex vivo applications of the instant invention.

Applicants also argue that the office did not present *prima facie* evidence as to why the office was of the opinion that a viral vector would not function as well as the plasmid vector was shown to function in cell culture. (See Response page 5, lines 7-8).

As discussed above, applicants have demonstrated the instant invention in cell culture and are therefore enabled for such. However, applicants are not enabled for any virus comprising (1) AchR (AA 1-210), (2) FasL and (3) truncated FADD, which are transfected into APCs as claimed in claim 58 specifically, as the virus may retain deleterious parts which may be rejected *in vivo* applications.

Therefore, as argued herein claims 41-67 stand rejected.

Conclusion

4. Claims 41-67 stand rejected.

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

6. Any inquiry concerning this communication should be directed to Eleanor Sorbello, who can be reached at (703)-308-6043. The examiner can normally be reached on Mondays-Fridays from 6.30 a.m. to 3.00 p.m. EST.

Questions of formal matters can be directed to the patent analyst, Tracey Johnson, whose telephone number is (703) 305-2982.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark, can be reached on (703) 305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER